

Role of different cytokines and seizure susceptibility: A new dimension towards epilepsy research

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Epilepsy is a common health problem. Although variety of factors influence the incidence and prevalence of seizures, cytokines are considered to play an important role in seizures. Cytokines are also known to be involved in other neurodegenerative disorders. Proinflammatory cytokines like IL-1, IL-6, TNF- α and growth factor vascular endothelial growth factor (VEGF) as well as anti-inflammatory cytokine IL-10 and related molecules have been described in CNS and plasma of experimental models of seizures and clinical cases of epilepsy. There are reports suggesting more predispositions to seizures during inflammatory conditions like colitis, pneumonia and rheumatoid arthritis. These inflammatory cytokines and growth factors are also known to have dual roles in affecting seizure susceptibility. It remains to be seen if cytokine modulators can be therapeutically exploited for patients with inflammatory disorder and suffering from epilepsy.

Keywords: Antiepileptic drugs, Cytokines, Epilepsy, Inflammation

Introduction

Epilepsy is a common health problem throughout the world. It affects more than 50 million people worldwide, 5 million of them have seizures more than once per month¹. Approximately 5-10% of the population usually develops seizure at least once during their lifetime, with the highest incidence occurring in early childhood and late adulthood². Variety of factors influence the incidence and prevalence of seizures. Reports suggest higher incidence of seizures among patients with chronic inflammatory problems compared to normal population³.

Cytokines are expressed at very low levels in healthy brain tissue under physiological condition, but they can be rapidly induced after a variety of stimuli. Several proinflammatory signals are rapidly induced in rodent brain during epileptic activity. These include cytokines, chemokines, prostaglandins, toll-like receptors, signal transduction pathways that recruit nuclear transcription factor kappa B (NF κ B), complement factors, and cell adhesion molecules⁴. It is still not clear whether these proinflammatory signals predispose to seizure or they are expressed following seizure. In addition, cytokines have been implicated as mediators of several forms of neurodegeneration in the brain. Sustained brain

inflammation may be an essential cofactor in Alzheimer disease and other neurodegenerative disorders such as Parkinson disease, dementia with lewy bodies, Huntington's and prion diseases⁵. Epileptic seizures cause severe and long-lasting events on the architecture of the brain, including neuronal cell death, accompanied neurogenesis, reactive gliosis, and mossy fiber sprouting. Neurotrophic factors are probable mediators of these pathophysiological events⁶. Proinflammatory cytokines inhibit neurogenesis and scar formation⁴. In this review role played by cytokines in the CNS, especially in pathogenesis and sequel of epilepsy is addressed. How peripheral inflammations like colitis, pneumonia increase the incidence of seizures and the effect of anti-inflammatory drugs on seizure is also attempted.

CNS and cytokines

Activation of the immune system is characteristic of host response to systemic infection, injury and inflammation. The development of an effective immune response involves lymphoid cells, inflammatory cells and hematopoietic cells. The complex interactions among these cells are mediated by a group of proteins collectively designated as cytokines which have role in cell to cell communication. Cytokines are low molecular weight regulatory proteins secreted by white blood cells and various other cells in the body in response to a number of stimuli⁷. In addition to various

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inflammatory properties, they have other functions. A number of cytokines play a significant role in the development of acute and chronic inflammatory response. Some of the common pro-inflammatory cytokines are interleukin-1 (IL-1), interleukin-2 (IL-2) interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and interleukin-12(IL-12)^{7,8}. There is a growing evidence to suggest involvement of cytokines in neurobiology⁹. Various features of inflammation like fever, altered neuroendocrine, cardiovascular and gastric function, increased metabolism, behavioral changes (for example anorexia, somnolence, reduced exploratory and sexual activity) can be mimicked by peripheral or central injection of cytokines, although they are much more effective when directly injected into brain^{10,11}. Cytokines have been reported to influence many central neurotransmitters including noradrenaline, 5-hydroxyl triptamine (5-HT), gamma amino butyric acid (GABA) and acetylcholine as well as expression of a number of neuropeptides (for example corticotropine releasing hormone, somatostatin, substance P, opioids, cholecystokinin and vasoactive intestinal peptide) in several brain regions^{12,13}. However, the relationship between each of the varied responses of the neurotransmitters and their relevance to specific cytokine action is yet to be defined. Similarly a number of second messenger systems in neurons are affected by cytokines including activation of cyclic adenosine monophosphate (cAMP), activity of protein kinase C, synthesis of nitric oxide, release of arachidonic acid and calcium influx. Neuronal function can also be influenced directly by glia² which is an important source and locus of action of many cytokines in the brain. Bacterial endotoxin and cytokines such as IL-1, TNF- α , interferons and macrophage colony stimulating factor (M-CSF) stimulate astrocytes and microglia to produce both themselves and other cytokines and also increase glial growth^{14,15}. Study reported IFN 2∞ can induce impairment of the GABAergic inhibitory control results epileptogenic effects¹⁶. Inflammatory cytokines and their receptors are present in various forebrain areas and both neurons and glia locally synthesize them^{15,17,18}. Inflammatory reactions occur in brain in various CNS diseases, including autoimmune, neurodegenerative, and epileptic disorders¹⁹.

Cytokines and seizure

Epileptiform phenomenon can be studied in experimental animals. Electrical stimulation as well as

chemicals and drugs can be used to produce seizures. Chemoconvulsants can be administered either systemically [pentylentetrazole (PTZ), picrotoxin, kainic acid] or topically (Alumina cream, Cobalt, Tungstic acid). There are indications that cytokines are involved in determining the neural excitability^{20,21}. IL-1 β and TNF- α contents were increased in the whole brain tissue after the rats were kindled by electrical stimulation of amygdala²². In addition, intraperitoneal TNF- α administration was followed by an increased susceptibility of amygdala to kindling²³. Moreover, there was an increase in IL-1 β level in the other experimental epilepsy models, and blockers of IL-1 β receptor had potent antiepileptic activity²⁴. All these data support the role of cytokines in convulsive and non-convulsive types of epilepsy.

Cytokines and related molecules have been described in CNS and plasma of experimental models of seizures and in clinical cases of epilepsy. Cytokine induction in brain after sustained seizures is dependent on the age and the appearance of cell injury in the rat²⁵. The cytokine expression in immature brain is associated specifically with cell injury rather than with seizures *per se*, suggesting that proinflammatory cytokines may contribute to the occurrence of status epilepticus (SE) induced hippocampal damage²⁶. There is a time-dependent, cell- and region-specific change in interleukin-1 receptor type I expression during status epilepticus. Interleukin-1 receptor type I in neurons mediates interleukin-1 β -induced fast changes in hippocampal excitability while interleukin-1 receptor type I in astrocytes mediate interleukin-1 β effects on neuronal survival in hostile conditions²⁷. Transcripts of interleukin-1 β , interleukin-6, interleukin-1 receptor antagonist and inducible nitric oxide synthase were significantly increased 2 h after status epilepticus in the stimulated hippocampus. Limbic seizures also rapidly and transiently enhanced IL-1 β , IL-6, and TNF- α mRNA in the hippocampus. But increase of IL-1Ra was delayed and was not produced in excess, as during peripheral inflammation²⁸. While multiple intracerebroventricular (ICV) injections of interleukin-1 receptor antagonist significantly decreased the severity of behavioral convulsions during electrical stimulation and selectively reduced TNF- α content in the hippocampus measured 18 h after status epilepticus suggesting that induction of spontaneously recurring seizures in rats involve the activation of inflammatory cytokines and related

pro- and anti-inflammatory genes in the hippocampus. These changes have an active role to play in hyperexcitability of the epileptic tissue²⁸.

Cytokines and neurodegenerative diseases

The inflammatory cytokines interleukin-1 β and TNF- α have been identified as mediators of several forms of neurodegeneration in the brain. Sustained brain inflammation may be an essential cofactor in Alzheimer's disease and other neurodegenerative disorders such as Parkinson disease, dementia with lewy bodies, Huntington's and prion diseases⁵. Brain inflammation in animal models of diseases like Alzheimer's, Parkinson's, and prion diseases is dominated by chronic microglial activation with minimal proinflammatory cytokine expression. However, these inflammatory cells amplify inflammatory responses to subsequent lipopolysaccharide challenges²⁹. It has been shown that neuroinflammatory stimuli which lead to elevation in cytokines may induce dopamine neuron cell loss in a NO-independent manner and contribute to Parkinson's disease pathogenesis³⁰.

Post-ischemic inflammation is a dynamic process involving a complicated set of interactions among various inflammatory cells and molecules. The resident inflammatory brain cells are activated in response to ischemic insults. As a result, several inflammatory genes are expressed. This leads to local generation of various cytokines, which in turn activate inflammatory signals³¹.

In Gauchers disease, there is accumulation of glucocerebroside or glucosylsphingosine due to glucocerebroside deficiency. They mediate brain inflammation in the mouse model via the elevation of proinflammatory cytokines, nitric oxide and reactive oxygen species³². Thus inflammatory cytokines are involved in various degenerative disorders, enzyme deficiency states and also following ischemia in brain.

Role of IL-1 in seizure — IL-1 cytokine family is an important regulator of immunological and inflammatory reactions. The two molecular forms are IL-1 α and IL-1 β . IL-1Ra binds to the same receptor and prevents the binding of either IL-1 α or IL-1 β . Intrahippocampal injection of IL-1 β worsened seizure activity, whereas IL-1Ra had a powerful anticonvulsant action in various models of limbic seizures. Excitotoxic stimuli increased the production IL-1 β in microglia-like cells in the hippocampus.

In addition, exogenous application of IL-1 β prolonged kainate-induced hippocampal EEG seizures by enhancing glutamatergic neurotransmission³³. In response to systemic kainic acid injection IL-1 β mRNA was rapidly induced. It was followed by induction of IL-1Ra mRNA and caspase-1 mRNA, supporting a role of the IL-1 system in the inflammatory response during excitotoxic damage³⁴. Excessive amounts of IL-1 β may influence the genesis of febrile convulsions, which has been postulated to occur by overproduction of IL-1 β , or by alteration in the IL-1 β /IL-1Ra ratio in the brain after an immune challenge³⁵. Focal cortical dysplasia and glioneuronal tumors are recognized causes of chronic intractable epilepsy. The expression of IL-1 β family members in these developmental lesions is thought to contribute to their intrinsic and high epileptogenicity³⁶. Circumstantial evidence suggests that IL-1 β and N-methyl-D-aspartate (NMDA) receptors can functionally interact. Exogenously applied IL-1 β prolongs seizures in an IL-1R type I-mediated manner. This effect depends on N-methyl-aspartate receptor activation. IL-1 β enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases³⁷.

Role of TNF- α in seizure — TNF- α is produced by wide cell types including macrophage, monocyte, T and B cells, NK cells and astrocytes. [TNF- α receptors include p60 (also called p55 or type I) and p80 (also called p75 or type II)]³⁸. TNF stimulates acute phase reaction. TNF- α activates proinflammatory signal transduction pathways in the hypothalamus of rats. These signaling events lead to the transcriptional activation of an early responsive gene and to the induction of expression of cytokines and a cytokine responsive protein such as IL-1 β , IL-6, IL-10 and suppressor of cytokine signalling-3³⁹. A relatively high concentration of mouse recombinant TNF- α (10 ng/ml) enhanced excitotoxicity when the cultures were simultaneously exposed to AMPA and to TNF- α . Decreasing the concentration of TNF- α to 1 ng/ml resulted in neuroprotection against AMPA-induced neuronal death independently on the application protocol⁴⁰. By using TNF- α receptor knock-out mice, it was demonstrated that the potentiation of AMPA-induced toxicity by TNF- α involves TNF receptor-1, whereas the neuroprotective effect was mediated by TNF receptor-2. Thus increased brain levels of TNF- α result in significant

inhibition of seizures in mice, and this action was mediated by neuronal p75 receptors. In addition, TNF- α induced the expression of neurotransmitters involved in the control of feeding and thermogenesis. Thus, TNF- α may act directly in the hypothalamus inducing a proinflammatory response and the modulation of expression of neurotransmitters involved in energy homeostasis.

Role of IL-6 and seizure — IL-6 also causes acute phase reaction. IL-6 protein levels are increased in cerebrospinal fluid in humans after recent tonic-clonic seizures. Since IL-6 and Leukemia Inhibitory Factor (LIF) transcripts were induced in the meninges after seizures, the protein products of these transcripts thought to be released in cerebrospinal fluid after seizures. In addition, the activity of IL-6 and LIF signaling pathways would be influenced by increased expression of their receptors after seizures⁴¹. In kainic acid-injected IL-6 null mice, reactive astrogliosis and microgliosis were reduced, while morphological hippocampal damage, oxidative stress and apoptotic neuronal death were increased⁴².

Role of IL-10 and seizure — The neuroprotective effect of IL-10 was attributed to inhibition of LPS-stimulated microglial activation. IL-10 significantly inhibited the microglial production of TNF- α , nitric oxide, ROS and superoxide free radicals after LPS stimulation⁴³.

Role of growth factors — Vascular endothelial growth factor (VEGF) is a vascular growth factor which induces the development of new blood vessels, vascular permeability, and inflammation. Recently, it has been shown to have a role as an inflammatory mediator. VEGF could also contribute to the inflammatory responses observed in cerebral ischemia. There was a striking increase in VEGF protein in both neurons and glia after pilocarpine induced status epilepticus in the brain. Increases in VEGF could contribute to the blood-brain barrier breakdown and inflammation observed after seizures. However, VEGF has also been shown to be neuroprotective across several experimental paradigms, and hence could potentially protect vulnerable cells from damage associated with seizures⁴⁴. Fibroblast growth factor-2 (FGF-2) is implicated in seizure susceptibility and in seizure-induced plasticity. Seizures increase FGF-2 mRNA and protein levels in specific brain areas and upregulate the expression of its receptor

FGFR-1. Short-term intrahippocampal injection of FGF-2 cause seizures, whereas long-term ICV infusion of low-dose FGF-2 does not affect kainate seizures but promotes behavioral recovery and reduces hippocampal damage⁴⁵. Dendritic accumulation of brain-derived neurotrophic factor (BDNF) mRNA and protein plays a critical role in the cellular changes leading to epilepsy. BDNF mRNA and protein accumulates in dendrites in all hippocampal subfields after pilocarpine seizures and in selected subfields after other epileptogenic stimuli (kainate and kindling)⁴⁶. BDNF activates its receptor, TrkB in the hippocampus during epileptogenesis. Activation of TrkB is required for epileptogenesis. BDNF regulates neuronal survival, differentiation and plasticity⁶. Glial-cell-line-derived neurotrophic factor (GDNF) is a potent survival factor for several types of neurons. GDNF serve to control KA-induced hippocampal cell loss and behavioral seizure⁴⁷.

Colitis and seizure

Yuhas, *et al.*⁴⁸ found that there was an involvement of TNF- α and IL-1 in the enhancement of PTZ induced seizures caused by *Shigella dysenteriae*. In an appropriate model the ability of bacterial product LPS to decrease the seizure threshold in mice was blocked by rabbit anti-murine TNF- α and anti murine IL-1 β antibodies in early stages of shigella gastroenteritis. These findings indicate that TNF- α and IL-1 β play a role in the very early sensitization of the central nervous system to convulsive activity after *Shigella dysenteriae* administration. It was suggested that similar mechanisms may trigger neurologic disturbance in other infectious diseases⁴⁸.

Phagocytosis of *Shigella* triggered TNF- α ⁴⁹ release and macrophages infected with invasive *Shigella* secreted large quantities of IL-1 β . There are several pathways by which TNF- α and IL-1 β can modulate the CNS function from periphery. There are evidence showing that variety of illness response such as fever, headache, slow wave sleep and behavioral changes which are governed by the brain are mediated by cytokines in the periphery which stimulate the CNS through afferent nerves⁵⁰. Alternatively some studies have demonstrated TNF- α and IL-1 β can cross the blood brain barrier⁵¹. They are also produced within the brain by glial cells.

To determine whether TNF- α and IL-1 β genes are expressed in the mice brain following peripheral administration of *Shigella dysenteriae* 60R. TNF- α and IL-1 β mRNA were induced in the brain, spleen and liver by 1 hour of injection of *Shigella dysenteriae* sonicate. The expression of TNF- α and IL-1 β mRNA in spleen, hippocampus and hypothalamus decreased after 6 h and again increased at 18 h post-injection. Local production of TNF- α and IL-1 β in the brain could be involved in enhanced seizure response of mice after administration of *Shigella dysenteriae*⁵⁰. It is, therefore, possible that TNF- α and IL-1 β produced locally in the brain are also involved in the sensitization to PTZ induced seizures by *Shigella dysenteriae*. To further elucidate the role of the host response in *Shigella*-related seizures, authors studied the ability of *Shigella dysenteriae* and its products to modulate seizures in C3H/HeJ [lps(d/d)] and in C3H/HeN [lps(n/n)] mice. Injection of *Shigella dysenteriae* 60R sonicate elevated plasma TNF- α and enhanced the convulsive response to PTZ in both mouse strains. Induced TNF- α levels were markedly lower in LPS-hyporesponsive C3H/HeJ mice than in LPS- responsive C3H/HeN mice. Watkins *et al*⁵⁰, demonstrated the crucial role of the host response with regard to the sensitivity to LPS, and specifically TNF- α production, in *Shigella* related seizures and lethality.

Certain activities of cytokines as mentioned earlier are modulated by the induction of secondary messengers such as nitric oxide. Pretreatment of mice with *Shigella dysenteriae* 60R sonicate elevated serum NO levels and enhanced the convulsive response to PTZ. Treatment of the mice with S-methylisothiourea sulfate, a potent inhibitor of inducible NO synthase, prevented the elevation of serum NO levels and concomitantly reduced the enhanced response to PTZ. In contrast, injection of N-nitro-L-arginine, a selective inhibitor of constitutive NOS, neither abolished the elevation of serum NO nor attenuated the enhancement of seizures. These findings indicate that NO, induced by *Shigella dysenteriae* 60R sonicate, is involved in enhancing the susceptibility to seizures caused by *Shigella dysenteriae*. It has been reported that TNF- α and IL-1 β synergistically mediate the neurotoxicity through NO induction⁵². NO also acts as a neurotransmitter and its overproduction have been linked to induction of seizures⁵³.

Another gene upregulated in the brain after systemic administration of either LPS or IL-1 β is the immediate early gene c-fos, which is activated during seizures⁵⁴. There are also evidence of functional connection between absence epileptic activity and LPS induction of prostaglandin synthesis and prostaglandin action⁵⁵.

Following induction of intestinal inflammation by administration of two daily doses of croton oil, there was alteration of seizure threshold, induced by PTZ in mice⁵⁶. While pretreatment with opioid receptors antagonist naltrexone restored the seizure threshold to normal levels, non-specific nitric-oxide synthase inhibitor N-nitro-l-arginine methyl ester and specific nitric oxide synthase inhibitor amino guanidine altered the seizure threshold in the control animals and mice treated with croton oil. Contrary to which, opioid system activity led to increased protection against PTZ induced clonic seizure threshold⁵⁷. But this is in accordance to previous studies demonstrating that opioid receptor agonists can affect seizure susceptibility in a biphasic manner causing dose dependent pro- and anti-convulsant effects, while high dose treatment with exogenous opioids may develop convulsions⁵⁷⁻⁵⁹. Naltrexone decreasing seizure threshold in intestinal inflammation points towards other central effects associated with opioid system. One possible mechanism linking the intestinal inflammation, opioids and altered seizure susceptibility consists of cytokines. Intestinal inflammation is associated with altered cytokine levels and activity^{60,61}. Opioids have wide range modulatory (including inhibitory and excitatory) effects on cytokine production and action^{62,63} and finally cytokines have been recently implied in the modulation of experimental seizure threshold^{49,62,63} as well as in various clinical settings associated with increased seizure susceptibility⁶⁴⁻⁶⁶.

Seizure in other inflammatory conditions

There are reports suggesting more predispositions to seizures during other inflammatory conditions. Seizures have also been reported to occur during the treatment of cancer with TNF- α or IL-1 β ⁶⁷ and in transgenic mice showing CNS specific expression of TNF- α ⁵¹. Foley *et al*⁶⁸ reported increased brain cytokines in feline infectious peritonitis. Infection at mucosal surface can lead to induction of pro-inflammatory cytokine production in the brain and these locally

synthesized mediators may contribute to the centrally controlled clinical manifestations of seizures in Bordetella pertussis infection⁶⁹. Rao *et al.*⁷⁰ showed that cytokines are rapidly induced in the brain following different peripheral inflammation which results decreased threshold to PTZ induced seizure.

Drugs and seizure

Anti-epileptic drugs affect the immune system. NFκB is essential to the expression of the kappa light chain of immunoglobulin and proinflammatory cytokines. Electrophoretic mobility shift assays of nuclear extracts demonstrated that sodium valproate inhibits NFκB activation induced by lipopolysaccharide, but the other anti-epileptic drugs diazepam, carbamazepine, phenobarbital, phenytoin do not⁷¹. Another study evaluated whether treatment with valproic acid or carbamazepine can modify interleukins and MCP-1 level in epileptic children and adolescents. At the end of one year therapy there was a significant increase in the production of interleukin-1α, interleukin-1β, interleukin-6, and monocyte chemoattractant protein-1; interleukin-2 production was significantly higher only in patients receiving carbamazepine⁷². An elevated level of proinflammatory cytokines may be responsible for the resistant epilepsy cases.

Conclusion

Normal brain is capable of having a seizure under certain circumstances like high fever. Patients with epilepsy can also develop seizures due to other precipitating factors. Precipitating factors can cause single seizure without epilepsy. Thus seizure result from a dynamic interplay between endogenous factors, epileptogenic factors, and precipitating factors². Many factors control neuronal excitability. Mechanisms intrinsic to the neuron include changes in conductance of ion channels, response characteristic of membrane receptor, cytoplasmic buffering, second messenger system and protein expression. Mechanisms extrinsic to neuron include changes in the amount of type of neurotransmitter present at the synapse, modulation of receptor by extracellular ion and by other molecule². Epilepsy *per se* is capable of elevation of cytokine. Also, patients with therapy resistant epilepsy display a pro-inflammatory profile of plasma cytokines produced by the brain itself⁷³.

But it has also been observed that elevated cytokines as during inflammation of brain or periphery decrease seizure threshold and predispose to epilepsy. Even antiepileptic drugs are known to elevate cytokines and predispose to resistant epilepsy. Thus role of cytokines has been increasingly recognized in the pathogenesis of epilepsy and growth factors have been implicated in synaptic plasticity.

Now the question arises how peripheral inflammation leads on to elevation of the cytokines in the brain thus predisposing to epilepsy. The peripheral inflammatory signal has to be communicated to the brain. The two possibilities are either the peripheral cytokines themselves are transported to brain or there is some afferent signaling which in turn upregulate the central inflammatory cascade to predispose to seizures. It is well known that stroke, traumatic brain injury, and central nervous system infections cause blood brain barrier (BBB) disruption. Marchi *et al.*⁷⁴ studied the effect of BBB disruption and epilepsy. In patients undergoing intraarterial chemotherapy, the incidence of seizure increased with the disruption of BBB. Thus inflammation causing disruption of BBB could accelerate the cytokine transport to the brain to cause seizure. Gallowitsch-Puerta *et al.*⁷⁵ reviewed recent advances related to the role of efferent vagus nerve-based mechanism termed as "the cholinergic anti-inflammatory pathway". It controls cytokines production and inflammation in neuroimmune interactions and prevents excessive inflammation. During endotoxemia, blockade of central muscarinic receptors reduced the inflammatory response. It can be further explored if modulation of this pathway has any effect on seizure threshold.

It has been argued that prolonged stimulation of proinflammatory signals by seizures or persistent proinflammatory situation in brain may lead to the establishment of pathologic substrate such as neurodegeneration, neuronal hyper excitability and blood brain barrier damage, contributing to epileptogenesis¹⁹.

The cytokines like TNF-α and growth factors like VEGF and FGF have a dual function, acting as proinflammatory and anti-inflammatory in different situations (Table 1). When monozygotic twins, discordant for epilepsy were compared with neurologically intact controls, it was found that they

Table 1 — Role of different cytokines and growth factors in seizure susceptibility

Tumour necrosis factor alfa (TNF α) ⁴⁰	Dual function: it is known to induce proinflammatory signal transduction pathway while relatively high concentration exert suppressive effect
Interleukin 1 β ³⁷	Enhance glutamergic transmission and NMDA receptor mediated intracellular calcium increase
Interleukin 6 ⁴²	Enhance sensitivity to the gluaminergic agonists and cause apoptotic neuronal loss
Interleukin 10 ⁴³	Neuroprotective: inhibiting synthesis of pro-inflammatory cytokines like Interferon- γ , IL-2, IL-3, TNF α and GM-CSF and also displays potent abilities to suppress the antigen presentation capacity of antigen presenting cells
Vascular endothelial growth factor (VEGF) ⁴⁴	Dual function: contribute to blood brain barrier breakdown and is also neuroprotective
Fibroblast growth factor (FGF 2) ⁴⁵	Enhance seizure susceptibility, also involved in seizure-induced plasticity and enhance angiogenesis
Brain derived neurotrophic Factor (BDNF) ⁶	Supports the survival of existing neurons, and encourages the growth and differentiation of new neurons and synapses
Glia cell line derived neurotrophic factor (GDNF) ⁷⁷	Supports the survival of dopaminergic and motoneurons
Leukemia Inhibitory Factor (LIF) ⁷⁸	Proinflammatory: LIF reduces neurogenesis in the olfactory bulb and subventricular zone by acting directly on neural stem cell; activates the Jak (Janus kinase)/STAT (signal transducer and activator of transcription) and MAP (mitogen-activated protein) kinase pathways
Nerve growth Factor (NGF) ⁷⁹	Rapid release of glutamate and an increase of Ca ²⁺ in cerebellar neurons through a p75-dependent pathway
Neurotrophin-3 (NT 3) ⁸⁰	Promote survival of pro-oligodendroblasts against glutamate-mediated apoptosis

had elevated levels of specific antibodies against ionotropic glutamate receptor of AMPA subtype 3 and other autoantibodies. Also both twins had significantly elevated levels of IFN- γ , TNF- α , IL-4 and IL-10 in the serum. But the serum levels of these cytokines were lower when compared to healthy sibling. Therefore, titer of such antibodies and these key cytokines could be crucial for either facilitating or arresting the development of epilepsy⁷⁶.

In diseases like rheumatoid arthritis and Chron's disease it is observed that cytokine i.e., TNF- α modulation are successful in their treatment. As experimental evidence suggests that most of these cytokines and growth factors act as double edge sword, it remains to be explored if modulation of cytokine can be exploited for the therapy of seizures in specific subgroup of population. Only with the advent of better research methodologies one can confirm the fine line between the beneficial and adverse effects of the cytokines in many of the conditions including epilepsy and thus exploit them therapeutically.

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